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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/357,704	07/20/1999	NEIL H. BANDER	242/024	9622

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EXAMINER	
HUNT, JENNIFER ELIZABETH	
ART UNIT	**PAPER NUMBER**
1642	17

DATE MAILED: 05/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/357,704	BANDER, NEIL H.	
	Examiner	Art Unit	
	Jennifer E Hunt	1642	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2001 has been entered.

2. Acknowledgement is made of applicant's cancellation of claims 1, 3-10, 12-19, and 68, and addition of new claims 69-126. Claims 69-121 are pending in the application and considered herein.

Claim Objections

Claim 117 is objected to because of the following informalities: Claim 117 depends from claim 159. This appears to be a typographical error. Appropriate correction is required. It is noted that the examiner has interpreted the claim to be dependent from claim 115.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 81-122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific deposited PSMA antibodies E99, J415, J533, and J591, does not reasonably provide enablement for any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies having variant or altered sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn a method of treating, preventing, or delaying development or progression of prostate cancer comprising providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, and administering the antibody or antigen binding portion thereof to a subject in need of treatment. The antibodies claimed encompass any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies which minimally contain incomplete portions of the disclosed antibodies, such as a single CDR which is shared, or antibodies having variant or altered sequences.

The specification discloses the specific deposited monoclonal antibodies E99, J415, J533, and J591. The specification fails to disclose specific guidance or working examples with regard to epitope mapping, or variations of the specific sequences of the disclosed antibodies, including CDR grafting and engineering of the claimed antibodies.

Epitope mapping and alterations of antibody structure are known to be complex and unpredictable. With regard to claims drawn to antibodies which bind to the epitope bound by antibodies E99, J415, J533, and J591, it would require undue experimentation to select and screen for these antibodies. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spatial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have

multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). The specification teaches a competitive binding assay of the antibodies E99, J415, J533, and J591, however, the results do not demonstrate what epitope is bound by the antibodies, or if another antibody could be produced which binds to the same epitope. As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Further, with regard to claims which recite antibodies which minimally contain "binding portions" of various antibody regions (claims 83-122), It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al

(Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of the E99, J415, J533, and J591 antibodies, in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function.

The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

Therefore, in light of the complexity of the art of epitope mapping and sequence variations and CDR alteration, the lack of guidance and working examples in the specification which would support such variants, and the breadth of the claims, one of skill in the art would not be enabled to practice the invention commensurate in scope with the claims.

5. Claims 69-126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of ablating or killing prostate cancer cells in vitro, does not reasonably provide enablement for a method of treating, preventing, or delaying development or progression of prostate cancer, including in vivo therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn a method of treating, preventing, or delaying development or progression of prostate cancer comprising providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, and administering the antibody or antigen binding portion thereof to a subject in need of treatment. The antibodies claimed encompass any antibody which binds the epitope bound by E99, J415, J533, and J591, or antibodies which minimally contain incomplete portions of the disclosed antibodies, such as a single CDR which is shared, or antibodies having variant or altered sequences.

The specification discloses the specific deposited monoclonal antibodies E99, J415, J533, and J591. The specification discloses 4 antibodies (E99, J415, J533, and J591) which were raised to the prostate cancer cell line LNcAP. The antibodies are shown to react strongly with prostate tissue and not normal tissue, and stain viable LNcAP cells. The J591 monoclonal antibody is shown to become internalized after binding viable LNcAP cells. Further, by immunoprecipitation, the antibodies are shown to bind identical bands as the PSMA specific antibody 7E11. Competition studies were performed between the new antibodies. Finally, the new antibodies were shown to bind to tumor vasculature in general in fixed tissue *in vitro* studies.

In addition, the specification provides evidence of the ability of the antibodies to target tissues *in vitro* for detection but provides insufficient objective evidence that antibodies to the PSMA extracellular domain, or the antibodies E99, J415, J533, and J591 effectively bind to cancerous prostate epithelial cells *in vivo*. Jain, R.K. et al., Cancer and Metastasis Reviews (IDS) teaches that the efficacy in cancer therapy of novel therapeutic agents such as monoclonal antibodies, cytokines, and effector cells has been limited by their inability to reach their target *in vivo* in adequate qualities. Three physiological factors responsible for poor localization of macro molecules in tumors have been identified: (I) heterogenous blood supply, (II) elevated interstitial pressure which lowers fluid extravasation, and (III) large transport distances in the interstitium. Furthermore, the average vascular surface area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also bind non-specifically to proteins

or other tissue components, bind specifically to the target and/or be metabolized which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of tumor vasculature and interstitium may also be responsible for poor delivery. Furthermore, it is well known in the art that the therapeutic effectiveness of immunotoxins is unpredictable. Generally, an effective therapeutic protocol for the treatment of a tumor, or the killing of cells in general is subject to a number of factors beyond simply the binding of a specific antibody to the marker antigen. Demonstration of antigen specificity in vitro cannot alone support operability for the method of killing of cells, including tumor cells, and prophylactic treatment of prostate cancer through administration of the antibody or antibody conjugates. In addition to the factors discussed previously, antigenic variables, such as intensity of antigen expression, heterogeneity of antigen expression, the chemical nature, location, and accessibility of the target antigen, as wells as antibody variables such as clearance mechanisms and persistence in tissues affect the outcome of *in vivo* based antibody methods.

Thus, the demonstration of in vitro binding to tissue samples provides insufficient objective evidence that the instant antibodies are predictably effective in ablating or killing cells in the in vivo clinical situation, based on in vitro binding to cells. Indeed, there is not indication that binding of J591 antibody to live LNcAP cells had any effect on their viability. The specification does not teach how to extrapolate data obtained by the immunohistochemical assays to the development of effective in

vivo mammalian therapeutic methods commensurate in scope with the claimed invention.

Furthermore, applicant has provided no evidence that the new antibodies bind to prostate tissue in vivo. As set forth above, *in vivo* antibody methods are unpredictable and generally lack correlation to *in vitro* results due to physiological, antigenic, and other factors. Therefore, absent evidence, it is not clear that the new antibodies would bind to any prostate material *in vivo*, and even if they did bind *in vivo*, it is not clear what they would bind to, or if said binding would be useful for cell killing or prophylactic treatment. Therefore it is not clear that a skilled artisan could predict the efficacy of the administration of agents or antibodies which bind the extracellular domain of PSMA to ablate or kill prostate cells based on the disclosure in the specification.

Furthermore, with regard to claims which recite prevention of prostate cancer, an effective protocol for the prevention of a tumor in a human patient is subject to a number of factors beyond simple administration of a composition comprising a relevant antibody in an acceptable formulation. Demonstrating tumor antigen specificity in vitro cannot alone support the predictability of the method for preventing said tumor growth through administration of an antibody which binds that antigen. The establishment and growth of a tumor is subject to variables beyond antigen specificity. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type of tumor (rapidly proliferating or slowly proliferating) and the tumor

burden. See Evans et al., QJM, June 1999, volume 92, No. 6, pages 299-307, who indicate that the goal of most vaccines is therapeutic efficacy- i.e. not sought to be developed to prevent the occurrence of cancer much as one would do with respect to infectious diseases (page 299, column 1 beginning of second section). Evans et al discuss various scenarios for combating cancer and it appears clear to one of skill in the art that cancer prevention is an unpredictable art and really varies from tumor to tumor and the knowledge of the availability of protective tumor antigens. Evans et al conclude that (page 303, last column) - that the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction.

Therefore, in light of the lack of guidance in the specification, with regard to treatment, prevention, and delayed development of prostate cancer, and further in light of the unpredictability and complexity of antibodies, cancer treatments and preventions, and in vivo therapy, one of ordinary skill in the art would not have been enabled to practice the full scope of the invention as claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national

> application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

7. Claims 69-70, 77-78, 95, and 97-100 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy et al., US Patent 6,150,508, filed November 21, 2000 (IDSAII.)

It is noted that Murphy et al. US Patent 6,150,508 is a continuation in part of application No. 08/827,017, filed March 25, 1997, which is a continuation in part of application No. 08/621,399, filed March 25, 1996. In order to qualify as prior art under 35 U.S.C. 102(e) over the instant claims, the disclosure of Murphy et al., US Patent 6,150,508 must have support to application 08/621,399, and thus the examiner has only cited the portions of Murphy et al., US Patent 6,150,508 which are supported by application 08/621,399.

Murphy et al., US Patent 6,150,508 teaches a method of treating prostate cancer tissue comprising providing an antibody or antigen binding portion thereof which binds to an extracellular domain of prostate specific membrane antigen, and administering it to a patient in need thereof to treat primary or metastatic prostate cancer (see abstract, column 6, lines 50-65, column 14, lines 40-56, and column 15, lines 10-14 and 35-47.) Although Murphy et al., US Patent 6,150,508 does not explicitly recite that the patient is a human, this is implicit in the disclosure, which discuses assays of human fluids, humanized antibodies, and tests the antibodies on a

human prostate epithelial cancer cell line (LNCAP), and thus the antibodies would function in humans, and would bind to prostate epithelial cells.

Murphy et al., US Patent 6,150,508 further teaches that the antibody can be included with a pharmaceutically acceptable carrier, excipient, or stabilizer (column 50, line 40,) that the antibody can be an antibody which binds live cells and /or is an IgG (column 9, line 50-column 10, line 16, column 7, lines 1-5,) that the antibody is a monoclonal antibody (column 6, lines 50-65,) that the antibody can be a Fab fragment, a $F(ab')_2$ fragment or an Fv fragment (column 10, line 35-55, column 11, lines 30-40, and column 14, lines 5-30.) Murphy et al., US Patent 6,150,508 further teaches that the antibody can be bound to a cytotoxic drug (column 14, lines 40-56), and that it can be bound to a fluorescent label or radiolabel (column 14, lines 5-30.)

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 69-78 and 95-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al., US Patent 6,150,508, patented November 21, 2000, in view of Thomas et al., Antibodies, A practical approach, Vol. 2, 1988, or Schlom et al. Molecular Foundations of Oncology, chapter 6, pages 95-134 (IDS AZ.)

Murphy et al., teaches as applied to claims 69-70, 77-78, 95, and 97-100. Murphy et al. fails to teach the specific techniques and antibody characteristics which are recited in the dependent claims, specifically, that the administration of the antibody is carried out parenterally, intravenously, by intracavity instillation, or rectally, that the antibody is internalized with the prostate specific membrane antigen, that the cytotoxic drug is one of a large number of known radiation emitters, or of bacterial, plant, or biological origin, where the antibody is effective to induce an endogenous or ADCC immune response, or that the antibody is administered with a second therapeutic modality.

These specific techniques and antibody characteristics are well known in the art, as set forth in applicant's disclosure of admitted prior art at pages 19-22, or as set forth for example in Thomas et al., Antibodies, a practical approach, Vol. 2, 1988 teaches that antibodies can be used for treatment, including conjugation to a cytotoxic substance. Also, Schlom et al. teaches that antibodies can be used for in treatment, including intravenous and intracavity administration, antibody internalization, and radiation emitters including short range radiation emitters, ^{125}I, ^{131}I or ^{99}mTc, or ^{111}I.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the treatments taught in Murphy et al., US Patent 6,150,508, with the art known techniques for therapy exemplified above and one would have been motivated to do so because these techniques are art recognized equivalents and variations for diagnosis and therapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
May 6, 2002

ANTHONY C. CAPUTA
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